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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GUPTA, ANISH	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 11/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,780	WAINWRIGHT ET AL.	
	Examiner	Art Unit	
	Anish Gupta	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71,72 and 80-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71,72 and 80-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The amendment filed, 9-7-04, is acknowledged. Claims 71, 80 and 82 were amended. Claims 71-72 and 80-83 are pending in this application.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

2. The rejection of claims 80-83 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is hereby withdrawn.

Claim Rejections - 35 USC § 102

3. The rejection of claims 71-72 and 82 rejected under 35 U.S.C. 102(b) as being anticipated by Harris et al. is hereby withdrawn.

Double Patenting

4. The rejection of claims 71-72, rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. US 6,222,021, is hereby withdrawn in view Applicants amendment.

5. Claims 80-83 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. US 6,222,021 in view of Oliveira et al. and Levin et al.. is hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 71-72 and 80-83 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Levin (US 3915805) et al. in view of Rice (US 4236893) for the reasons set forth in the previous office action and the reasons set forth below.

The claims are drawn to a biosensor device comprising an endotoxin binding protein from horseshoe crab *Limulus polyphemus*, immobilized on a solid phase support, which is either quartz or silicon and a method of determining endotoxins in a sample.

Applicants argue that Levin is directed to an in-vitro turbidity assay for detecting endotoxin. Nowhere does the reference disclose the use of an endotoxin binding protein immobilized on a solid support. Rice does not cure the deficiency of Levin because the reference discloses the use of antibodies in a sample using antigen coated piezoelectric oscillator. There is no disclosure of the use of endotoxin binding protein immobilized on a solid support. Applicants state that there is no suggest or motivation to combine these references. Applicants argue that assuming arguendo that the statement, the association between horseshoe crab and endotoxin is similar antibody/antigen binding, is correct, it does not automatically render the references combinable. "Instead, the proper test is whether there is specific motivation or suggest in Levin to modify Levin with the method of Rice." Since such a motivation has not be identified in the rejection, a *prima facie* case of obviousness has not been establish. Finally, there is no reasonable expectation of success. The Examiner has not provide any objective evidence that supports successful modification of the turbidity assay of Levine using the methods taught by Rice.

Applicants arguments, filed 9-7-04, have been fully consider but have not been found persuasive.

Applicants state that the rejection has not provided any motivation. To the contrary, Rice teaches that piezoelectric oscillator means of analysis is inexpensive and unsophisticated and the results obtained are "rapid, accurate and objective measurements." (see col. 2, lines 59-68). This is the basis of using a piezoelectric oscillation method. Furthermore, Rice discloses a variety of different antibody/antigen relationship type agents that can be used. The reference states that not only antibodies but other binding reagents such as bacterium Straphlococcus aureus or other cells which have surface receptors for certain types of immunoglobulins can be used (see col. 2, lines 46-

59). Since the reference disclose that structurally distinct binding partners can be used, one would expect protein in the amebocytes of the horseshoe crab can also be used.

Furthermore, Applicants argue that the reference do not provide an reasonable expectation of success. To the contrary, the reference of Rice discloses numerous means of conjugating the antigen onto the oscillator, including "conventional techniques known in the art for attaching proteins to solids." (see col. 4, lines 25-35). Thus, one of ordinary skill in the art would know how to conjugate the protein in the amebocytes of the horseshoe crab to the oscillator. Secondly, in a piezoelectric oscillator detection method, the measurement is conducted, as indicated in Rice by :

> "Piezoelectric oscillators are commonly used in electronic equipment or clocks as frequency standards and controllers. Generally, they consist of a small quartz wafer (or other material), having metal electrodes deposited on either side and some means provided for making electrical contact with an oscillator circuit. When placed in such a circuit, the portion of the wafer located between the electrodes vibrates with the precise natural frequency of the wafer. A given mass coupled to the electrode of the oscillator or crystal (used interchangeably herein) causes a decrease in the initial frequency of the crystal in an amount proportional to the mass added. Shons et al supra describe a direct method for measuring the amount of an antibody in a liquid sample using a piezoelectric quartz crystal. The crystal is first coated with the antigen specific for the antibody being assayed and its frequency measured. The coated crystal is then exposed to the sample containing the antibody. The change in frequency of the crystal due to antibody pickup is a direct measurement of the amount of total antibody in the sample."

As stated in the previous office action, the interaction between the protein from the Limulus polyphemus and endotoxin is similar to an antibody/antigen relationship. That is, the protein from the Limulus polyphemus binds with the endotoxin. Note that primary reference states that the protein from Limulus polyphemus reacts with the endotoxin in a sample resulting in an increase in turbidity or viscosity (see col. 3, lines 1-15 and claim 1). Further, Applicant's specification acknowledges this interaction, on page 3 of the specification, where it is taught the interaction between the Limulus polyphemus protein and endotoxin result in clot formation. Thus, one would

expect, once the Limulus polyphemus protein is bound to the quartz oscillator, to interact with the endotoxin thereby changing the mass of the electrode and changing the frequency of the crystal. Note that Levin et al. teach the Limulus polyphemus protein can detect can detect as little as five ten thousandths microgram of endotoxin per milliliter and thus is an effective means of measuring endotoxin.

In conclusion, the combination of references provides ample motivation and reasonable expectation of success and thus establishes a prima facie case of obviousness.

The rejection is maintained.

7. Claims 71-72 and 80-83 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Levin (US 3915805) et al. in view of Olivera et al. (US4242096) for the reasons set forth in the previous office action and the reasons set forth below.

The claims are drawn to a biosensor device comprising an endotoxin binding protein from horseshoe crab *Limulus polyphemus*, immobilized on a solid phase support, which is either quartz or silicon and a method of determining endotoxins in a sample.

Applicants argue similar points for Levin in view of Olivera as they did for Levine in view of Rice. Applicants argue that Levin is directed to an in-vitro turbidity assay for detecting endotoxin. Nowhere does the reference disclose the use of an endotoxin binding protein immobilized on a solid support. Olivera does not cure the deficiency of Levin because the reference discloses the use of antibodies in a sample using antigen coated piezoelectric oscillator. There is no disclosure of the use of endotoxin binding protein immobilized on a solid support. Applicants state that there is no suggest or motivation to combine these references. Applicants argue that assuming arguendo that the statement, the association between horseshoe crab and endotoxin is similar antibody/antigen

binding, is correct, this does not automatically render the references combinable. "Instead, the proper test is whether there is specific motivation or suggest in Levin to modify Levin with the method of Rice." Since such a motivation has not be identified in the rejection, a *prima facie* case of obviousness has not been establish. Finally, there is no reasonable expectation of success. The Examiner has not provided any objective evidence that supports successful modification of the turbidity assay of Levine using the methods taught by Rice.

Applicants arguments, filed 9-7-04, have been fully consider but have not been found persuasive.

Applicants state that the rejection has not provided any motivatio. To the contrary, Olivera et al. states that piezoelectric oscillator is a method that is simple and uses inexpensive instrumentation (see col. 3, lines 12-15). Further, the method does not involve labeling techniques or the problems therewith (see col. 3, lines 26-35). The reference states that the method can be used for analysis of a variety of antigenic materials ranging from low molecular weigh to compounds to large macromolecules (see col. 3, lines 36-40). Thus, the motivation to use a piezoelectric oscillator is that it is simple and uses inexpensive instruments without involving labeling techniques or the problems therewith.

Applicants argue that the reference do not provide an reasonable expectation of success. To the contrary, the reference of Olivera discloses numerous means of conjugating the antigen onto the oscillator, including "conventional techniques known in the art for attaching proteins to solids." (see col. 4, lines 52-60). Thus, one of ordinary skill in the art would know how to conjugate the protein in the amebocytes of the horseshoe crab to the oscillator. Secondly, in a piezoelectric oscillator detection method, the measurement is conducted, as indicated in Olivera involves the following :

> "Piezoelectric oscillators have previously been used for the direct measurement of antibodies. In J. Biomed. Mater. Res., Vol. 6, pp. 565-569(1972) Shons et al describe coating a piezoelectric oscillator with specificproteins. The protein-coated oscillator is then placed in a sample containing an unknown quantity of the corresponding antibody to the protein. As the antibody binds to the oscillator, there is a downward shift in the frequency of the oscillator. The concentration of antibody in the sample can be calculated by reference to a standard curve.."

As stated in the previous office action, the interaction between the protein from the Limulus polyphemus and endotoxin is similar to an antibody/antigen relationship. That is, the protein from the Limulus polyphemus binds with the endotoxin. Note that primary reference states that the protein from Limulus polyphemus reacts with the endotoxin in a sample resulting in an increase in turbidity or viscosity (see col. 3, lines 1-15 and claim 1). Further, Applicant's specification acknowledges this interaction, on page 3 of the specification, where it is taught the interaction between the Limulus polyphemus protein and endotoxin result in clot formation. Furthermore, Olivera et al. states that the method disclosed can be used for analysis of a variety of antigenic materials ranging from low molecular weigh to compounds to large macromolecules (see col. 3, lines 36-40). Thus, one would expect, once the Limulus polyphemus protein is bound to the quartz oscillator, to interact with the endotoxin thereby resulting downward shift in the frequency of the oscillator. Note that Levin et al. teach the Limulus polyphemus protein can detect can detect as little as five ten thousandths microgram of endotoxin per milliliter and thus is an effective means of measuring endotoxin.

In conclusion, the combination of references provides ample motivation and reasonable expectation of success and thus establishes a prima facie case of obviousness.

The rejection is maintained.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback , can normally be reached on (571) 272-0961. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Anish Gupta
Patent Examiner